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Efficacy of remdesivir in hospitalized nonsevere COVID-19 patients in Japan: A large observational study using the COVID-19 Registry Japan

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Abstract

Objectives: Although several randomized controlled trials have compared the efficacy of remdesivir with that of placebo, there is limited evidence regarding its effect in the early stage of nonsevere COVID-19 cases.

Methods: We evaluated the efficacy of remdesivir on the early stage of nonsevere COVID-19 using the COVID-19 Registry Japan, a nationwide registry of hospitalized COVID-19 patients in Japan. Two regimens (start remdesivir therapy within 4 days from admission vs. no remdesivir during hospitalization) among patients without the need for supplementary oxygen therapy were compared by a three-step processing (cloning, censoring, and weighting) method. The primary outcome was a supplementary oxygen requirement during hospitalization. Secondary outcomes were 30-day in-hospital mortality and the risk of invasive mechanical ventilation or extracorporeal membrane oxygenation (IMV/ECMO).

The data of 12,487 cases met our inclusion criteria. The “start remdesivir” regimen showed a lower risk of supplementary oxygen requirement (hazard ratio: 0.850, 95% confidence interval [CI]: 0.798–0.906, p value < 0.001). Both 30-day in-hospital mortality and risk of IMV/ECMO introduction were not significantly different between the two regimens (hazard ratios: 1.04 and 0.983, 95% CI: 0.980–1.09 and 0.906–1.07, p

values: 0.210 and 0.678, respectively).

Conclusions: Remdesivir might reduce the risk of oxygen requirement during hospitalization in the early stage of COVID-19; however, it had no positive effect on the clinical outcome and reduction of IMV/ECMO requirement.

Keywords: COVID-19, Remdesivir, Inverse-probability treatment weighting

Introduction

As in other parts of the world, the number of COVID-19 patients is increasing in Japan, with 1,069,554 cases and 15,330 deaths being reported from January 14, 2020, to August 12, 2021 (n.d.). In addition to the treatment of the hyperinflammatory state and coagulopathy, antiviral medication is one of the important components of COVID-19 treatment (Cevik et al., 2020). Among the antiviral medications for SARS-CoV-2, only remdesivir was approved in Japan on May 7, 2020 (Pharmaceuticals and Medical Devices Agency, n.d.).

Several randomized controlled trials (RCTs) have compared the efficacy of remdesivir with that of placebo. In an RCT in China that enrolled hospitalized COVID-19 pneumonia patients with hypoxia, no statistically significant clinical benefits were observed (Wang et al., 2020). A multinational RCT (ACTT-1) conducted in Europe, the United States, and Asia including Japan (Saito et al., 2021) confirmed that remdesivir shortened the time to recovery in hospitalized COVID-19 patients with pneumonia (Beigel et al., 2020). However, in the subgroup analysis, no reduction in the time to recovery was observed in patients who were intubated or on extracorporeal membrane oxygenation (ECMO) at the time of drug administration. Additionally, there was no reduction in time to recovery in the subgroup of patients with no oxygen requirement (RR for time to-recovery 1.29 (95% CI: 0.91-1.83)). Although the recovery rate improvement observed among patients enrolled from Asia was similar to that among the overall population, ethnically Asian patients did not show such treatment benefit. The multinational SOLIDARITY Trial, organized by the World Health Organization, demonstrated no survival benefit for remdesivir in hospitalized COVID-19 patients (WHO Solidarity Trial Consortium et al., 2020). The trial enrolled 61% of patients from Asia and Africa in total, but no patients from Japan were enrolled. In another RCT conducted in the United States, Europe, and Asia including 16%–19% Asians, no statistically significant difference was observed between the 10-day remdesivir group and the standard treatment group (Spinner et al., 2020). These data indicate conflicting results regarding remdesivir's clinical efficacy, and currently, recommendations in the guidelines of remdesivir use against COVID-19 are inconsistent and its optimal role remains uncertain (World Health Organization).

Although the efficacy of remdesivir against severe COVID-19 cases has been already examined in several studies, its efficacy against nonsevere cases or cases in the early stage of disease has not yet been evaluated. In the study of Spinner et al. (Spinner et al., 2020), patients with COVID-19 pneumonia were targeted with preserved room-air oxygen saturation. However, the interpretation of the results of this trial is limited by the inconsistent evidence of the treatment regimens.

We conducted this study to evaluate the efficacy of remdesivir in nonsevere COVID-19 patients in the early stage of disease, especially the stage before the initiation of supplementary oxygen therapy and other pharmaceutical treatment.

Methods

Study population and data

We used the data of patients derived from COVIREGI-JP (Matsunaga et al., 2020). The inclusion criteria are both (1) a positive SARS-CoV-2 test (PCR test and/or rapid antigen test) and (2) inpatient treatment at a healthcare facility. SARS-CoV-2 testing is based on the notification criteria of the Infectious Diseases Law (Ministry of Health, Labour, and Welfare). Patients who refused to participate in the study by opting out were excluded.

We had modified a case report form of the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) (International Severe Acute Respiratory and Emerging Infection Consortium). Study data were collected and managed using REDCap (Research Electronic Data Capture), Associates and Clinicians

(JCRAC) data center of the National Center for Global Health and Medicine.

We used data from cases that had entered all the following major items as of April 30, 2021 (i.e., frozen data as of April 30, 2021), for this study, similar to the previous report (Matsunaga et al., 2020): basic information at admission (demographics and epidemiological characteristics), comorbidities, signs and symptoms at the time of admission (including conditions at admission), outcome at discharge, supportive care during hospitalization, history of drug administration during hospitalization, and complications during hospitalization.

Study design

Eligibility for analysis set

Among all patients registered as cases of COVIREGI-JP, we excluded non-Japanese and <18-year-old cases to evaluate the efficacy of remdesivir in the Japanese adult cohort. We also excluded patients with severe diseases who had already been initiated on supplementary oxygen therapy during admission and/or admitted more than 4 days before the day of symptom onset to evaluate the efficacy of remdesivir in the early stages of treatment.

Endpoints, treatment strategies of interest and follow-up

The primary outcome was oxygen therapy requirement during 30 days of admission. The secondary outcomes were 30-day fatality risk and risk of IMV or ECMO. We compared the following treatment regimens: Regimen 1, start remdesivir therapy within 4 days from the day of admission for at least 3 days and at the most 15 days without the combination of systemic steroids and some immunosuppressive agents or antivirals (tocilizumab, baricitinib, and favipiravir), and Regimen 2, not using remdesivir, other immunosuppressive agents or antivirals (tocilizumab, baricitinib, and favipiravir), and systemic steroids during their admission. Other supportive treatments were allowed in both regimens. The indication of remdesivir as defined by Ministry of Health, Labour and Welfare is as follows: i) oxygen saturation ≤ 94% (ambient air), ii) requirement of supplementary oxygen/IMV/ECMO, and iii) pneumonia due to SARS-CoV-2 (added from January 2021).

Each patient was followed up until 30 admission days, event of interest (initiation of oxygen therapy for primary analysis, death, or initiation of IMV/ECMO within 30 admission days for secondary analysis), and discharge, whichever came first. Furthermore, we required both regimens withhold the initiation of supplementary oxygen therapy for 4 days from admission to evaluate the efficacy of remdesivir among patients without the need for intensive therapy at admission. We excluded patients who were initiated on oxygen therapy within 4 days from admission; the possible time-related biases associated with such exclusion after admission (the start of follow-up) (Hernán et al., 2016; Suissa and Dell'Aniello, 2020) were addressed by the novel statistical approach described in the next section.

Statistical analysis

To compare the abovementioned treatment regimens from time-varying remdesivir treatment data in an unbiased manner, we used the 'three-step' method (cloning, censoring, and weighting) (Hernán, 2018). First, we prepared clones (or data copies) of patients to assign them to the two regimens on the person-day basis. We assigned each person to the treatment regimens at admission at which the 'eligibility' of enrollment was judged. We assigned patients treated with remdesivir at Day 1 to the 'start remdesivir' regimen arm and other patients to both regimens. Assigning a patient to both arms simultaneously is equivalent to having two clones of that patient in the dataset, with each copy assigned to a different arm. The cloning process was performed only once before censoring.

Second, we artificially censored the clones if they deviated from their assigned regimen during the follow-up period. For instance, consider a patient who was initiated on remdesivir between days 1 and 4; his/her clone assigned to Regimen 2 ('no remdesivir') was censored at that time, but the clone assigned to Regimen 1 ('start remdesivir') was followed up thereafter. Conversely, for a patient not initiated on remdesivir at Day 5, his/her clone assigned to Regimen 1 was censored at Day 5, but the clone assigned to Regimen 2 was followed up thereafter. In addition, clones were censored at any time when the following conditions were met: (1) supported by supplementary oxygen before 4 days from admission, (2) treated with systemic steroids, (3) treated with tocilizumab, (4) treated with baricitinib, (5) treated with favipiravir, (6) duration of remdesivir treatment shorter than 3 days (patients were censored when they discontinued remdesivir before the 3 days elapsed from treatment initiation), and (7) duration of remdesivir treatment longer than 15 days (patients were censored at 15 days if they continued using remdesivir). Moreover, when we compared the primary outcome (supplementary oxygen requirement), patients were excluded from the risk set at the next day of the beginning day of oxygen administration. Similarly, when we compared the secondary outcomes, IMV/ECMO introduction and death within 30 days from admission were the signs of censoring. Discharged patients were censored from the next day of discharge. We set the duration of observation as 30 days, and all patients were censored after 30 days have elapsed since their admission. The process of cloning and censoring is shown in Figure 1.

(Figure 1)

Third, to eliminate selection bias due to the abovementioned artificial censoring, we used the inverse probability of censoring/discharge weights (Robins and Finkelstein, 2000). The weights of each person-day were calculated using pooled logistic regression models for being censored or discharged, such as age, sex, cardiovascular diseases, chronic respiratory diseases, diabetes mellitus, severe renal diseases (serum creatinine level: ≥3 mg/dl) or dialysis, hypertension, hyperlipidemia, obesity diagnosed by physicians, solid tumor, days from symptom onset to admission, use of corticosteroids, use of anticoagulants (time-independent variables), and National Early Warning Score (NEWS, time-dependent variable) (The National Health Service England, n.d.). The models were fitted separately according to regimens and follow-up days. The weights were stabilized according to the regimen-day-specific probability without covariate and were multiplied until that day of the follow-up. Especially, we had only intermittent data about the clinical course of the patient. In this study, we had information of patients at days 1, 4, 8, 15, 22, and 29. For example, a patient’s record indicating administered oxygen at Day 8 implies that oxygen support for that patient began between days 5 and 8 and the exact day is not available. We used NEWS at Day 1 as that of Day 1; NEWS at Day 4 as that of days 2, 3, and 4; NEWS at Day 8 as that of days 5, 6, 7, and 8; and NEWS at Day 15 as that of days 9, 10, 11, 12, 13, 14, and 15, same as NEWS at days 22 and 29. These possible confounders were selected for their potential association with the outcome of interest based on clinical knowledge and previous studies (Cunningham et al., 2020; Lighter et al., 2020; Petrilli et al., 2020; Tartof et al., 2020; Williamson et al., 2020; Wu and McGoogan, 2020).

Finally, the discrete-time hazard ratio of primary and secondary outcomes between two regimens was estimated using weighted pooled logistic regression included primary, secondary, and tertiary terms of days as covariates. As each patient has multiple lines in the dataset (each day, each regimen of the same patient until censored), we used cluster-robust standard errors regarding each patient as a cluster to estimate 95% confidence intervals (CIs). We also estimated cumulative incidence rates under the two regimens by multiplying the weighted probabilities of no-event using the Kaplan-Meier method. The pointwise 95% CIs at each day were based on 2.5 and 97.5 percentiles of 1000 bootstrap estimates. All statistical analyses were conducted using R, version 4.1.2 (R Core Team, 2018).

Results

The data of 12,487 of 16,747 cases met our inclusion criteria. Table 1 describes the basic characteristics of the included cases. A total of 824 patients were treated with remdesivir, and the treatment duration depended on each facility and physician's decision. The duration of remdesivir treatment was 5 days in 485 cases (58.9%). The 10-day regimen was completed in 105 cases (12.7%). A total of 115 patients (14.0%) were administered remdesivir for <5 days, and 88 (10.7%) were administered between 6 and 9 days. A total of 27 patients (3.3%) were administered for >10 days. Inappropriate duration (smaller than zero) was recorded for three patients, and then they were excluded from the final analysis. Patients in the case group were older, more frequently male and more severe and fatal.

(Table 1)

Table 2 shows the characteristics of the patients at the beginning of the observation, after weighted by inverse probability of censoring or discharge.

(Table 2)

Regimen 1 (treated with remdesivir within 4 days of admission) showed a lower risk (adjusted hazard ratio: 0.850, 95% CIs: 0.798–0.906, $p < 0.001$) of supplementary oxygen requirement than Regimen 2 (treated without remdesivir). However, the 30-day fatality risk and risk of IMV/ECMO introduction were not different between the two groups (adjusted hazard ratio: 1.04 [95% CIs: 0.9806–1.09] and 0.983 [95% CIs: 0.906–1.07], *p* values: 0.217 and 0.678, respectively). Table 3 shows the details of primary and secondary outcomes.

(Table 3)

Figure 1 shows the daily cumulative probability of presenting primary and secondary outcomes. The distribution of inverse probability weights is shown in Supplementary Figure S1.

(Figure 2)

(Figure S1)

Regarding the safety of remdesivir treatment, 92 of 824 (11.2%) cases reported adverse events (Table 4), of whom 24 (26.1%) were considered as having probable relevance to remdesivir. Although 66 patients (71.7%) continued remdesivir treatment despite adverse events, the remaining 26 (28.3%) suspended their treatment. A total of 45 patients (48.9%) had liver dysfunction or liver enzyme elevation, 10 (10.9%) reported renal dysfunction, 3 (3.3%) had nausea/vomit, and 4 (4.3%) showed rash. No patient had sequelae due to adverse events.

(Table 4)

Discussion

Our study showed that remdesivir administration in the early stage of disease might reduce the supplementary oxygen requirement during hospitalization. However, it did not reduce fatality risk and risk of IMV/ECMO requirement in hospitalized COVID-19 patients. These results concerning fatality and IMV/ECMO are compatible with a previous study(WHO Solidarity Trial Consortium et al., 2020) and support that remdesivir is not an essential drug for COVID-19-specific treatment, as suggested by the latest clinical guideline (CDC, 2020; Ministry of Health, Labour, and Welfare., n.d.; World Health Organization, n.d.). Similarly, this study demonstrated the possible benefit of using remdesivir in the early stage of the disease. Our results suggest that among nonsevere hospitalized patients (i.e., patients without oxygen requirement), early initiation of remdesivir is beneficial.

However, further discussion would be desirable because our analysis demonstrated that the drug of interest did not improve the final prognosis of the disease. Although the risk of severe adverse events due to remdesivir appears to be low, we can consider it as an unnecessary risk if the drug does not improve the outcome. Conversely, substantial benefit can be obtained by reducing the burden on healthcare facilities if it prevents COVID-19 patients from the need for supplementary oxygen therapy.

Furthermore, we must note the fact that the healthcare system in Japan allowed us to hospitalize even nonsevere patients. For instance, Japanese indications for hospitalization are quite different from those of other countries (Ministry of Health, Labour, and Welfare., n.d.; National Institutes of Health, n.d.; World Health

Organization, n.d.); therefore, it is difficult to apply our results directly to different settings. In addition, the hospitalization criteria in Japan have been changing over the COVID-19 pandemic time (Yamada et al.). Initially, the indication of remdesivir in Japan was limited to severe COVID-19 cases (Ministry of Health, Labour, and Welfare., n.d.). Remdesivir was approved in Japan in May 2020 by the fast-track approval followed by the US FDA Emergency Use Authorization (Commissioner, 2020). At that time, the indication of remdesivir was limited to severe cases whose oxygen saturation was ≤94% (ambient air) and who required supplementary oxygen or IMV/ECMO. In January 2021, the Ministry of Health, Labour, and Welfare in Japan extended its indication to “patients who have pneumonia due to SARS-CoV-2 infection.” Consequently, the number of mild or moderate cases administered remdesivir increased recently, and it enabled us to analyze the efficacy of remdesivir in the early stage of disease. Further evaluation in other healthcare settings will be one of the future challenges.

Our study has some limitations. The most important one is that it is not an RCT but a retrospective cohort study. Certainly, we sincerely attempted to adjust various factors that affect clinical outcomes; however, our method does not enable us to adjust all the numerous confounding factors (Rosenbaum and Rubin). Although our method enables us to adjust time-dependent factors and immortal time bias (Hernán, 2018; Hernán et al., 2016), we could not include time-dependent variables other than NEWS. Moreover, as our data are based on a registry system, it is difficult to interpret several items. For instance, “fatality” in this study implies that a patient died during his/her 30-day observation period, i.e., during hospitalization. Even if a patient died after he/she was discharged, we labeled this patient as a survived one. The cause of death is also unavailable from the registry data, and when a fatal case has a serious comorbidity such as cancer, we are not aware of the disease that caused death to the patient. Furthermore, COVIREGI-JP does not collect information about the daily clinical status of each patient. The adverse events of remdesivir were reported based on researchers’ decisions and thus might be underreported. Nevertheless, our data at least appropriately adjust the time-independent characteristics of cases associated with clinical outcomes (e.g., age, comorbidity, etc.) and an important time-dependent factor deeply associated with their clinical course and outcome (i.e., NEWS); hence, we believe that the results were reliable.

For the evaluation of drug safety, we must consider that our registry contains limited data about adverse events, especially the relationship between symptoms and drugs. However, considering only some adverse events and no reported sequelae, we can consider remdesivir to be a relatively safe drug.

Conclusions

Remdesivir might reduce supplementary oxygen requirement during hospitalization.

However, it showed no positive effect on the clinical outcome.

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Ethics

This study was approved by the NCGM ethics review (NCGM-G-003494-0).

Information regarding opting out of our study is available on the registry website.

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.
The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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Figure 1. Flaw diagram of the cloning process

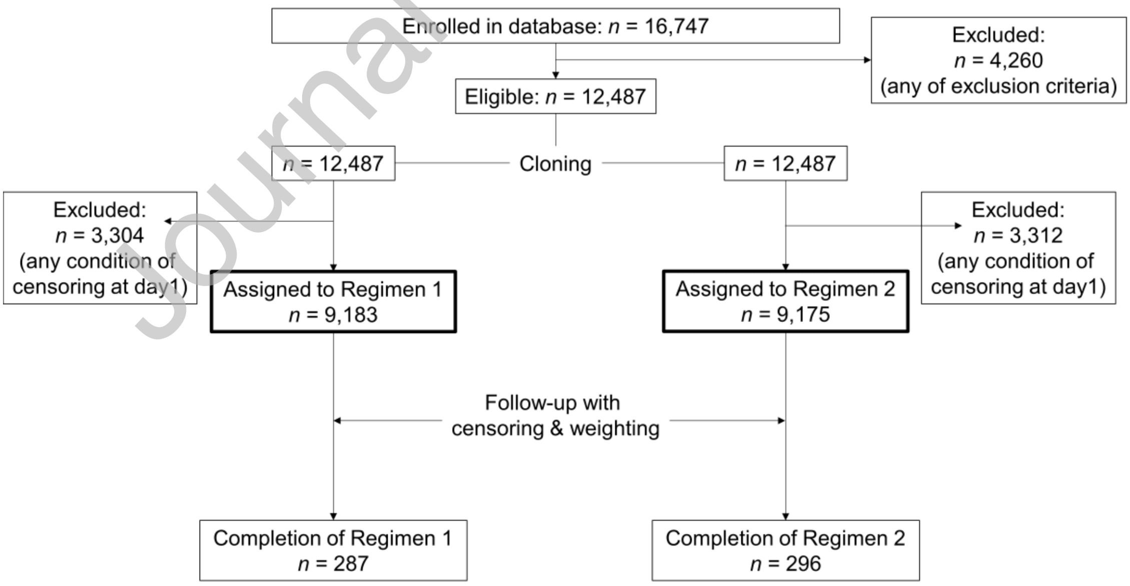

Figure 2. Daily cumulative probability of presenting primary/secondary outcomes

Panel A: daily cumulative probability of not being supported by oxygen

Panel B: daily probability of survival

Panel C: daily cumulative probability of not being supported by invasive mechanical ventilation (IMV)/extracorporeal membrane oxygenation (ECMO)

Red ribbons represent Regimen 1 (treated with remdesivir) and blue ribbons represent Regimen 2 (treated without remdesivir). Shaded zones represent pointwise 95% confidence intervals by bootstrapping.

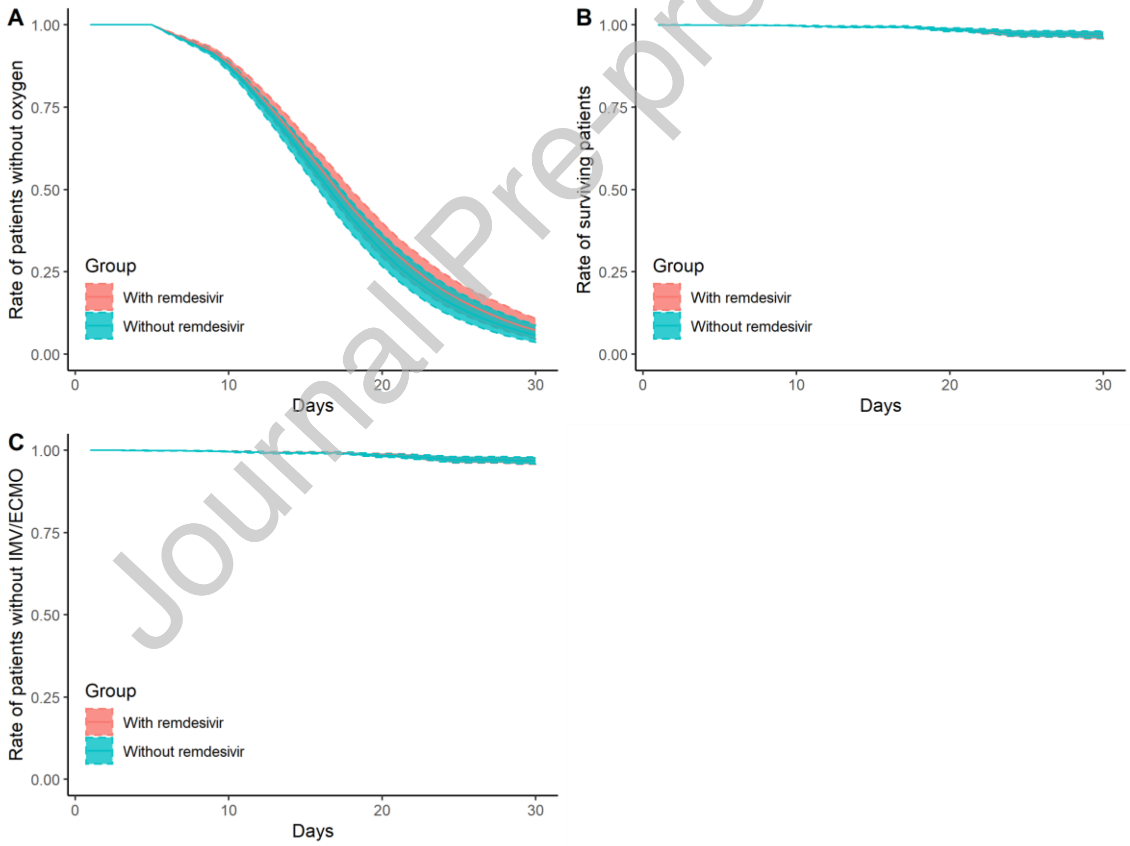

Table 1 Basic characteristics of patients who met the inclusion criteria

	Patients initiated	Patients without	Total (n =

	on remdesivir (n = 824)	remdesivir (n = 11,663)	12,487)
Age (years)	68 [56–79]	51 [34–71]	52 [35–71]
Male	5,32 (64.6%)	6,176 (53.0%)	6,708 (53.7%)
Cardiovascular disease	57 (6.9%)	547 (4.7%)	604 (4.8%)
Respiratory disease	34 (4.1%)	268 (2.3%)	302 (2.4%)
Diabetes mellitus	225 (27.3%)	1,415 (12.1%)	1,640 (13.1%)
Severe renal disease or dialysis	19 (2.3%)	200 (1.7%)	219 (1.8%)
Hypertension	367 (44.5%)	2845 (24.4%)	3212 (25.7%)
Obesity	90 (10.9%)	809 (6.9%)	899 (7.2%)
Charlson Comorbidity Index	1 [0–2]	0 [0–1]	0 [0–1]
NEWS at Day 1	1 [0–2]	1 [0–2]	1 [0–2]
NEWS at Day 4	2 [1–4]	1 [0–2]	1 [0–2]
NEWS at Day 8	2 [1–4]	1 [0–2]	1 [0–2]

NEWS at Day 15	2 [1–4]	1 [0–2]	1 [0–3]
NEWS at Day 22	3 [1–5]	1 [0–3]	1 [0–3]
NEWS at Day 29	11 [9–13]	9 [9–11]	9 [9–11]
Fatal cases	69 (8.4%)	285 (2.4%)	354 (2.8%)
Oxygen administration during hospitalization*	559 (67.8%)	1784 (15.3%)	2343 (18.8%)
IMV/ECMO during hospitalization	48 (5.8%)	98 (0.8%)	146 (1.2%)
Days from symptom onset to hospitalization	3 [1–4]	3 [1–4]	3 [1–4]
Use of systemic steroids	666 (80.8%)	1840 (15.8%)	2506 (20.1%)
Use of favipiravir	264 (32.0%)	2926 (25.1%)	3190 (25.5%)
Use of tocilizumab	63 (7.7%)	100 (0.9%)	163 (1.3%)
Use of baricitinib	0 (0%)	0 (0%)	0 (0%)
Days from onset to remdesivir	6 [4–9]	NA	NA

administration			
Days from admission to remdesivir administration	5 [3–10]	NA	NA
Duration of remdesivir administration 5 days	485 (58.9%)	NA	NA

Numbers in brackets represent percentage and interquartile range.

NA, not available; NEWS, National Early Warning Score; IMV/ECMO, invasive mechanical ventilation/extracorporeal membrane oxygenation

*Indication for supplementary oxygen was judged by each physician

Table 2. Characteristics of the patients after weighted by inverse probability of censoring/discharge at the beginning of the observation

	Regimen 1 (treated with remdesivir)	Regimen 2 (treated without remdesivir)	Standardized mean difference
Number	9183	9175	
Age (years)	50.3 (21.5)	50.2 (21.5)	0.004

Male	52.3%	52.5%	0.002
Cardiovascular disease	4.1%	4.1%	<0.001
Respiratory disease	2.0%	2.0%	0.003
Diabetes mellitus	10.4%	10.4%	<0.001
Severe renal disease or dialysis	1.3%	1.3%	0.002
Hypertension	21.3%	21.1%	0.006
Obesity	6.5%	6.5%	0.003
Charlson Comorbidity Index	0.45 (0.95)	0.45 (0.95)	0.001
NEWS at Day 1	1.02 (1.17)	1.01 (1.17)	0.002
NEWS at Day 4	1.18 (1.34)	1.18 (1.34)	0.001
NEWS at Day 8	1.28 (1.58)	1.28 (1.57)	0.001
NEWS at Day 15	1.62 (2.01)	1.63 (2.02)	0.004
NEWS at Day 22	1.88 (2.39)	1.87 (2.38)	0.005
NEWS at Day 29	10.11 (1.92)	10.13 [1.96]	0.011

Fatal cases	1.7%	1.7%	<0.001
Oxygen administration during hospitalization*	9.4%	9.4%	0.001
IMV/ECMO during hospitalization	0.5%	0.5%	0.001
Days from symptom onset to hospitalization	2.62 (1.60)	2.62 (1.60)	<0.001
Use of systemic steroids	9.6%	9.5%	0.005
Use of favipiravir	9.4%	9.4%	0.002
Use of tocilizumab	0.4%	0.4%	<0.001
Use of baricitinib	0 (0%)	0 (0%)	<0.001

Regimen 1: treated with remdesivir

Regimen 2: treated without remdesivir

Continuous variables are presented mean (standard deviation). Categorical variables are presented in percentage

NEWS, National Early Warning Score; IMV/ECMO, invasive mechanical ventilation/extracorporeal membrane oxygenation

Table 3 Results of pooled logistic regression analysis on the effect of remdesivir on primary and secondary outcomes

	Person-days	Event	Weighted event rate (per 1,000 person-day)	Hazard ratio	95% CI	*P* value
Oxygen requirement						
Regimen 1	85,129	324	3.81	0.850	0.798–0.906	<0.001
Regimen 2	85,606	379	4.43	1	Reference	
30-day fatality risk						
Regimen 1	85,129	33	0.388	1.04	0.980–	0.2170

					1.09	
Regimen 2	85,606	33	0.385	1	Reference	
IMV/ECMO*						
Regimen 1	85,129	42	0.493	0.983	0.906–1.07	0.678
Regimen 2	85,606	44	0.514	1	Reference	

Regimen 1: treated with remdesivir

Regimen 2: treated without remdesivir

CI, confidence interval; IMV/ECMO, invasive mechanical ventilation/extracorporeal membrane oxygenation

Table 4. Adverse events during remdesivir treatment

Severity	Number of cases	Probable relevance to remdesivir	Cessation of remdesivir	Sequelae
Mild	69 (8.4%*)	16 (23.2%)	17 (24.6%)	0 (0%)
Liver dysfunction (38)				

Renal failure (14)				
Other (17)				
Moderate				
Liver dysfunction (5)				
Renal failure (4)	20 (2.4%*)	7 (35.0%)	8 (40.0%)	0 (0%)
Rash (3)				
Other (8)				
Serious				
Renal failure (2)	3 (0.4%*)	1 (33.3%)	1 (33.3%)	0 (0%)
Neutropenia (1)				

*Denominators are the total number of cases treated with remdesivir (n = 824)

Mild: adverse events need no treatment or presented no symptom

Moderate: adverse events need non-invasive treatment

Serious: important adverse events need invasive treatment